REMARKS

The examiner rejects claims 1-6 under 35 USC §103(a) as unpatentable over Baert et al. (US 6,365,188 - "Baert '188" herein) in view of Klimesch et al. (US 4,880,585). This rejection is respectfully traversed. To make a *prima facie* case of obviousness, the prior art must teach or suggest each claim element, give some suggestion or motivation to make the claimed invention, and also give a reasonable expectation for success in doing so (*see, e.g., In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). The cited references do not meet these requirements.

The Baert '188 does not teach or suggest each element of the present claims. The melt-extrusion mixture in Baert '188 includes the active ingredient, one or more cyclodextrins, and optional "suitable" additives (col.4:14-42). The reference expressly identifies anti-oxidants, pigments, flavors, stabilizers, preservatives, buffers, and plasticizers as being "suitable" for purposes of the melt-extrusion process (col.4:24-42). Notably absent from this list are binders such as those of the present invention. Such binders are introduced into the pharmaceutical dosage forms of Baert '188 *only after* the melt-extrusion step has been completed, and the extrudate has been cooled and milled (col.11:7-9). Accordingly, Baert '188 does not teach the presently claimed process.

Further, one of skill in the art would conclude from this disclosure that binders should be excluded from the melt-extrusion mixture, where cyclodextrins are present. In addition to the above-indicated omission of binders as "suitable" additives for the melt-extrusion mixture, and the example of their use being restricted solely to a mixture with the cooled and milled extrudate, knowledge held by one of skill in the art supports their exclusion. Where an active ingredient and a cyclodextrin are introduced separately into a process, rather than as a pre-formed complex, it is desirable for the process to be performed in such a way as to ensure that these ingredients react to form a complex.

In Baert '188, binders are specifically omitted from the listing of suitable additives for the melt-extrusion step itself. However, such binders are employed later, and therefore have some value in the process. In considering Baert '188, one of skill in the art would most likely conclude that binders were excluded from the melt-extrusion step due to their tendency to compete with the cyclodextrin in complexing with the active ingredient, thus lowering the amount of the desired inclusion complex. Such a conclusion is reasonable and likely given the disclosure and examples in the reference, and the knowledge of one of ordinary skill in the art.

As Klimesch is employed simply to teach the direct tableting of the melt-extrusion, it does not make up for the deficiencies in the Baert '188 reference. These combined disclosures neither teach nor suggest the direct tableting of a melt-extrusion mixture containing an active ingredient, a cyclodextrin, and a binder, as in the present

claims. Accordingly, applicants respectfully request that the rejection of claims 1-6 based on Baert '188 and Klimesch be withdrawn.

The examiner also rejects claims 1-6 under 35 USC §103(a) as obvious over Baert '188 in view of Schultz et al. (US 6,194,395), optionally in view of a second reference to Baert et al. (US 6,342,245 - "Baert '245" herein). This rejection is likewise respectfully traversed. Again, to make a *prima facie* case of obviousness, the prior art must teach or suggest each claim element, give some suggestion or motivation to make the claimed invention, and also give a reasonable expectation for success in doing so (*see, e.g., In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). The cited references do not meet these requirements.

Baert '188 is discussed above, and does not teach or suggest the presently claimed invention.

Schultz discloses a similar process to that of Baert '188, and also fails to teach or suggest the present invention. In this reference, the melt-extrusion mixture is made up of an active ingredient, cyclodextrins, and "other optional additives" (col.5:55-57). The nature of these "other optional additives" is not disclosed. After melt-extrusion, the mixture is cooled and prepared into pellets by milling, and once milled, the extrudate "may be admixed with various excipients," including binders, "to prepare conventional solid pharmaceutical dosage forms" (col.5:59 to col.6:6; col.6:27). This process for

producing a solid dosage form is exemplified in the reference, through a constructive example, which gives various amounts for the ingredients in the milled extrudate, and also for various excipients, including crospovidone (col.6:23-40).

In Schulz, the capacity for cyclodextrins to form inclusion complexes, and the "concomitant solubilizing properties," are expressly discussed (col.2:11-13). Given that the solubility of the active ingredient increases with the presence of cyclodextrin in Schultz, one of skill in the art would conclude that these components form inclusion complexes (col.7:28-43). Accordingly, the same conclusion would be derived from this reference as from Baert '188, namely that binders are excluded from the melt-extrusion mixture due to their potential competition with cyclodextrins in binding to the active ingredient.

Baert '245 does not counter the above-identified conclusion drawn from the disclosures of Baert '188 and Schultz. In Baert '245, the melt-extrusion mixture contains an active ingredient, a water-soluble polymer, and optional additives (col.1:14-16; col.7:56-58). The nature of these optional additives is not discussed, and yet, it is evident that cyclodextrins are specifically excluded as being unnecessary (col.2:22-30). Accordingly, Baert '245 not only fails to disclose the presently claimed invention, but also specifically teaches away from melt-extruding a mixture containing both cyclodextrin *and* a polymer such as the presently claimed binders.

Combining this teaching with the teachings of Baert '188 and Schultz, described above, one of skill in the art would most likely conclude that *either* cyclodextrins *or* the

disclosed water-soluble polymers would be useful for melt-extruding an active ingredient, but not both together. In the case of Baert '188 and Schultz, the water-soluble polymers corresponding to the present binders would compete with the cyclodextrin in binding to the active ingredient. In the case of Baert '245, use of cyclodextrin is the prior art to be avoided. The combined disclosure of these references neither teaches nor suggests the direct tableting of a melt-extrusion mixture containing an active ingredient, a cyclodextrin, and a binder, as in the present claims. Accordingly, applicants respectfully request that the rejection of claims 1-6 based on Baert '188, Schultz, and Baert '245 be withdrawn.

In view of the foregoing remarks, applicants consider that the rejections of record have been obviated and respectfully solicit passage of the application to issue.

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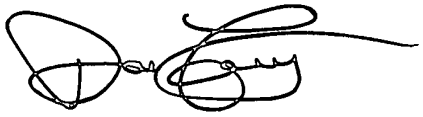
Respectfully submitted,
KEIL & WEINKAUF



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COMPLETE LISTING OF ALL CLAIMS IN APPLICATION

1. (previously presented) A process for producing solid dosage forms which are suitable for oral or rectal administration for humans and animals, wherein

   a) 0.5 to 30% by weight of at least one active ingredient which is uncomplexed by cyclodextrin,

   b) 0.5 to 70% by weight of at least one cyclodextrin selected from the group consisting of α-, β-, γ- or δ-cyclodextrins, the reaction products of cyclodextrins with alkylene oxide, alkyl halides, dialkyl sulfates, carbonyl chlorides, epihalohydrines, isocyanates or halogenated carboxylic acids, and polymer-modified cyclodextrins,

   c) 10 to 98% by weight of at least one polymeric binder, selected from the group consisting of polyethylene glycol having a molecular weight above 4000, polyvinylpyrrolidone, and copolymers comprising N-vinylpyrrolidone and vinyl acetate, and

   d) 0 to 50% by weight of conventional excipients

   are mixed and plasticized at a temperature below 220°C without adding a solvent and the resulting plastic mixture is shaped to produce the dosage form.

2. (original) A process as claimed in claim 1, wherein the molar ratio between active ingredient and cyclodextrin is in the range from 0.1 to 4.0.

3. (previously presented) A process as claimed in claim 1, wherein the plastic mixture is shaped in a molding calendar to produce the dosage forms.

4. (original) A process as claimed in claim 3, wherein a molding calender with counterrotating molding rolls is used, with at least one of the molding rolls having on its surface depressions to receive and shape the plastic mixture.

5. (previously presented) A solid dosage form which is essentially free of aliphatic C_2-C_8-di- and -tricarboxylic acids and aromatic C_6-C_{10}-monocarboxylic acids, obtainable by a process as claimed in claim 1.

6. (original) A solid dosage form as claimed in claim 5, wherein at least 10% by weight of the active ingredient are present in the form of a cyclodextrin/active ingredient complex.